

**REMARKS/ARGUMENTS**

***I. Status Of The Claims***

Upon entry of the above amendment, Claims 1-6 and 8-24 are pending in this application. Claims 1 and 21 are amended to recite "a co-solvent selected from one or more of the group consisting of aromatic and polyhydric alcohols present in an amount of less than approximately 10% by weight." Support is found in Example formulas 1-11 on pages 7-12. As such, Applicants believe no new matter has been entered with the foregoing amendments. Reconsideration is respectfully requested.

***II. Rejections under § 103***

***A. Kasting (U.S. 5,041,439) by itself or in view of Yu (U.S. 5,571,841) or Weiner (WO 97/12602)***

Applicants respectfully traverse the rejection of Claims 1-6, 8-9, 12-19 and 21-23 as allegedly being obvious over Kasting alone, Kasting in view of Yu, or Kasting in view of Weiner, because the cited disclosures, alone or combined, do not teach or suggest a pharmaceutical composition as recited in currently amended independent Claims 1 and 21. For example, the compositions disclosed in columns 11 and 12 of the Kasting patent have a polyhydric alcohol in an amount of 30% to 97.75%. Yu does not cure this deficiency of Kasting, because the exemplified minoxidil formulations of Yu have 15% and 16% polypropylene glycol (Examples 3 and 4; column 7, line 50 through column 8, line 6 of the Yu patent). The inclusion of Weiner also does not cure this deficiency of Kasting, because Weiner does not disclose or suggest formulation parameters.

Furthermore, Kasting and Weiner teach away from the presently claimed formulations. In constructing this rejection, the Examiner has disregarded components deemed critical by Kasting and Weiner for the efficacious delivery of minoxidil, and which are not required components of the presently claimed formulations. A prior art reference must be considered in its entirety, including portions that would lead away from the claimed invention. M.P.E.P. 2141.02, citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540.

For instance, the Kasting formulation requires combining minoxidil with a penetration-enhancing vehicle consisting of a C<sub>3</sub>-C<sub>4</sub> diol or a C<sub>3</sub>-C<sub>6</sub> triol *and* a C<sub>16</sub> or C<sub>18</sub> mono-unsaturated or branched polar lipid alcohol, because “it is only by utilizing these specifically-defined C<sub>16</sub> or C<sub>18</sub> alcohols that vehicles exhibiting improved skin penetration...can be formulated” (*see*, column 4, lines 38-45 and the penetration study data presented in the tables in column 13, line 1 through column 14, line 16). The Kasting data teaches away from formulations that include minoxidil without also including a C<sub>16</sub> or C<sub>18</sub> mono-unsaturated or branched polar lipid alcohol. As the claims in the Kasting patent demonstrate, the Kasting patent is enabled *only* for formulations containing a penetration-enhancing carrier having a small polar solvent *and* a polar lipid alcohol.

Likewise, the Weiner formulation requires that minoxidil reacted with an acid or base is encapsulated in lipid vesicles (*see*, page 4, lines 13-18 of the Weiner publication). The data presented in Example 3 shows that minoxidil reacted with lactic acid, but not encapsulated in a lipid vesicle, is essentially undeliverable into hairless rat skin, whereas lipid vesicle encapsulated lactic acid-treated minoxidil penetrated living skin strata more deeply than the other tested formulations (please compare formulations III and XI in Table 1, on page 6 in the “Living Skin Strata” column and review the paragraph on page 7, lines 9-17 of the Weiner publication). Based on this data, those of skill in the art certainly would have no motivation to react minoxidil with an acid, but not encapsulate the minoxidil salt in a lipid vesicle.

To the extent that acid salts are mentioned in Kasting and Weiner at all, each of these references teach that reaction of minoxidil with an acid alone is *insufficient* to achieve therapeutic skin penetration, because the crux of their inventions resides in the further inclusion of a polar lipid alcohol or encapsulation in a lipid vesicle. Therefore, the combined formulations of Kasting, or Kasting and Yu *must* possess a penetration enhancer consisting of a polar solvent *and* a polar lipid alcohol and the combined formulation of Kasting and Weiner must include a penetration enhancer consisting of a polar solvent *and* a polar lipid alcohol and be encapsulated in a lipid vesicle. By contrast, the claimed homogeneous pharmaceutical compositions of the present invention comprise a mineral acid or an organic acid, but do not require a penetration enhancer consisting of a polar solvent *and* a polar lipid alcohol, or encapsulation in a lipid

vesicle. Based on the disclosures of Kasting and Weiner, one of skill in the art would expect the present pharmaceutical compositions to be ineffective in the percutaneous delivery of a piperidinopyrimidine derivative, such as minoxidil. Accordingly, the disclosures of Kasting and Weiner require additional elements and teach away from the present pharmaceutical compositions.

In view of the foregoing, the disclosure of Kasting alone, or Kasting combined with Yu or Weiner does not teach or suggest the pharmaceutical compositions recited in independent Claim 1 and dependent Claims 2-6, 8-9 and 12-19 that comprise a piperidinopyrimidine derivative or a pharmaceutically acceptable salt thereof and an aromatic or polyhydric alcohol co-solvent present in an amount of less than approximately 10% by weight. Similarly, Kasting alone, or Kasting combined with Yu or Weiner also does not teach or suggest methods that comprise providing a pharmaceutical composition that comprises an aromatic or polyhydric alcohol co-solvent present in an amount of less than approximately 10% by weight, as is recited in independent Claim 21, and dependent Claims 22-23. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection.

***B. Kasting (U.S. 5,041,439) by itself or in view of Yu or Weiner, and further in view of Uchikawa (U.S. 5,156,836)***

The Examiner has rejected Claims 10-11, 20 and 24 by the further inclusion of Uchikawa. Claims 10-11 and 20 depend from independent Claim 1, so therefore include all the limitations of Claim 1. Likewise, Claim 24 depends from independent 21, and includes all the limitations of Claim 21. Neither Claim 1 nor Claim 21 have been included in this rejection.

The Examiner cites Uchikawa for disclosing benzyl alcohol as part of a long list of general purpose components and one of three potential alcohols (*see*, column 4, lines 7-33, especially lines 9-11 and 31-32 of the Uchikawa patent). Uchikawa also discloses minoxidil as part of this long list of general components, but does not disclose minoxidil or any other piperidinopyrimidine derivative anywhere else, much less disclose or suggest any particular formula having minoxidil or a piperidinopyrimidine derivative (column 4, line 19).

If anything, combining Uchikawa with Kasting alone, Kasting and Weiner or Kasting and Yu describes a composition that requires yet additional components deemed essential by the inventor. In particular, Uchikawa considers including an amine oxide and an anionic surfactant essential to their hair tonic composition (*see*, column 4, lines 7-9), but does not consider minoxidil essential. As Claim 1 indicates, the Uchikawa hair tonic composition requires an amine oxide and an anionic surfactant (*see*, column 11, lines 50-53). Therefore, a minoxidil composition described by the combined disclosures of Kasting and Uchikawa or Kasting, Yu and Uchikawa must necessarily include a penetration enhancer consisting of a polar solvent *and* a polar lipid alcohol, an amine oxide and an anionic surfactant. Similarly, a minoxidil composition described by the combined disclosures of Kasting, Weiner and Uchikawa must possess a penetration enhancer consisting of a polar solvent *and* a polar lipid alcohol, an amine oxide and an anionic surfactant, and be encapsulated in a lipid vesicle.

The combined compositions proposed by the Examiner in combining Kasting, Uchikawa and Yu or Weiner are not the claimed invention. The pharmaceutical compositions recited in Claims 1, 10, 11 and 20 do not require a penetration enhancer consisting of a polar solvent *and* a polar lipid alcohol, or an amine oxide and an anionic surfactant, or lipid vesicle encapsulation. The methods of treatment recited in Claims 21 and 24 comprise providing a composition that does not require a penetration enhancer consisting of a polar solvent *and* a polar lipid alcohol, or an amine oxide and an anionic surfactant, or lipid vesicle encapsulation.

In view of the foregoing, the Examiner is respectfully requested to withdraw this rejection.

***C. Bazzano (U.S. 5,183,817) or in view of Yu or Weiner***

The Examiner has rejected Claims 1-6, 8-9, 12-19 and 21-23 as allegedly being obvious over Bazzano in view of Yu or Weiner. Applicants respectfully traverse this rejection, because the disclosures of Bazzano and Yu or Bazzano and Weiner, teach away from the presently claimed formulations. In constructing this rejection, as with the rejection above, the Examiner has disregarded components deemed critical by Bazzano and Weiner for the

efficacious delivery of minoxidil, and which are not required components of the claimed formulations. As stated above, a prior art reference must be considered in its entirety, including portions that would lead away from the claimed invention. M.P.E.P. 2141.02.

Specifically, the Bazzano formulation requires a retinoid to aid in percutaneous absorption of minoxidil, because “neither compound [minoxidil or a retinoid] alone may have profound effects on advanced alopecias” (*see*, column 5, lines 16-29; Table II and corresponding analysis in column 23, line 34 through column 24, line 5 of the Bazzano patent). The Bazzano data teaches away from using minoxidil without a retinoid. As the claims in the Bazzano patent demonstrate, the Bazzano patent is enabled only for formulations containing a minoxidil compound and a retinoid.

Likewise, as submitted above, the Weiner formulation requires that minoxidil reacted with an acid or base is encapsulated in lipid vesicles (*see*, page 4, lines 13-18 and page 6, Table 1 of the Weiner publication). For reasons analogous to those discussed above, the minoxidil compositions proposed by the Examiner based on the combined disclosures of Bazzano and Yu must possess a retinoid. Furthermore, Yu does not bring Bazzano closer to the claimed pharmaceutical compositions or methods, because the Yu formulations require 15-16% propylene glycol. Similarly, minoxidil compositions described by the combined disclosures of Bazzano and Weiner must possess a retinoid and be lipid encapsulated. The proposed compositions based on the combined disclosures of Bazzano and Yu, or Bazzano and Weiner require additional components deemed essential to the efficacious delivery of minoxidil, but that are not required in the claimed compositions or the claimed methods. Therefore, the combined disclosures of Bazzano and Yu or Bazzano and Weiner can not properly render Claim 1-6, 8-9, 12-19 and 21-23 obvious. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection.

***D. Bazzano in view of Yu or Weiner, and further in view of Uchikawa***

The Examiner has rejected Claims 10-11, 20 and 24 by the further inclusion of Uchikawa. As above, neither Claim 1 nor Claim 21 have been included in this rejection.

This rejection is respectfully traversed, because, as submitted above, Uchikawa requires the inclusion of the additional components of an amine oxide and an anionic surfactant, that are deemed essential by Uchikawa. Therefore, the combined formulations of Bazzano, Yu and Uchikawa proposed by the Examiner require a retinoid, an amine oxide and an anionic surfactant. Similarly, the combined compositions of Bazzano, Weiner and Uchikawa proposed by the Examiner require a retinoid, an amine oxide and an anionic surfactant, and encapsulation in a lipid vesicle. For the reasons analogous to those submitted above, the combined disclosures of Bazzano, Yu and Uchikawa and Bazzano, Weiner and Uchikawa require additional elements in their minoxidil compositions not required in the claimed pharmaceutical compositions or claimed methods, and therefore can not properly render Claims 1, 10-11, 20, 21 and 24 obvious. In view of the foregoing, the Examiner is respectfully requested to withdraw this rejection.

***E. Navarro (WO 97/03638) in view of Weiner***

The Examiner has rejected Claims 1-6, 8-9, 12-19 and 21-23 as allegedly being obvious over Navarro in view of Weiner. Applicants respectfully traverse this rejection, because, unlike the claimed pharmaceutical compositions and methods, the combined compositions of Navarro and Weiner require  $\gamma$ -cyclodextrin and encapsulation in a lipid vesicle.

Navarro discloses using  $\gamma$ -cyclodextrin to decrease the amount of polyalcohol solvent, such as propylene glycol, and provide a formulation that does not leave hair with a greasy feeling (*see*, page 2, line 31 through page 3, line 13 of the Navarro publication).<sup>1</sup> Navarro does not disclose or suggest decreasing the percentages of a polyhydric alcohol without replacing it with  $\gamma$ -cyclodextrin. The inclusion of  $\gamma$ -cyclodextrin is critical to Navarro's compositions. Examples 1-3 on page 5, lines 6-35, disclose formulations with varying amounts of  $\gamma$ -cyclodextrin and propylene glycol. Example 4 on page 6, lines 1-7, discloses a formulation without  $\gamma$ -cyclodextrin. In Example 5, Navarro discloses that formulations 1-3 were the most interesting, and that comparative formula 4 was problematic in that it left hair greasy, among other shortcomings (*see*, page 6, lines 25-33). Based on the disclosure of Navarro, one skilled in

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<sup>1</sup> A computer-generated translation from [www.freetranslation.com](http://www.freetranslation.com) is provided in Appendix A.

the art would not be motivated to prepare a minoxidil composition with less than about 10% propylene glycol without also adding a compensating amount of  $\gamma$ -cyclodextrin. Claims that issued from the Navarro PCT application in EP Patent No. 0 841 892 B1 are directed to compositions that requires  $\gamma$ -cyclodextrin.<sup>2</sup>

Therefore, the combined disclosures of Navarro and Weiner describe a minoxidil composition that requires  $\gamma$ -cyclodextrin and encapsulation in a lipid vesicle. Like the proposed combinations above, the combined disclosures of Navarro and Weiner describe a composition that requires additional components not required in Claims 1-6, 8-9, 12-19 and 21-23. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

***F. Navarro in view of Weiner, and further in view of Uchikawa***

The Examiner has rejected Claims 10-11, 20 and 24 by the further inclusion of Uchikawa. As above, neither Claim 1 nor Claim 21 have been included in this rejection.

As discussed above, the further inclusion of Uchikawa describes a minoxidil formulation that is further adrift from the claimed compositions because Uchikawa requires additional essential components not required in the instant pharmaceutical compositions and methods. The Examiner's proposed combination of Navarro, Weiner and Uchikawa describe a minoxidil composition that requires  $\gamma$ -cyclodextrin, an amine oxide and an anionic surfactant, *and* encapsulation in a lipid vesicle. Because the compositions and methods of Claims 1, 10-11, 20-21 and 24 recite pharmaceutical compositions that require fewer components than the proposed combined composition of Navarro, Weiner and Uchikawa, their combined disclosures can not properly render these claims obvious. Therefore, Applicants respectfully request the Examiner to withdraw this rejection.

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<sup>2</sup> English claims of EP 0 841 892 B1 are attached as Exhibit B.

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Amdt. dated February 20, 2004  
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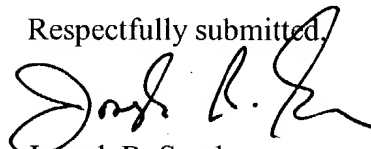
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### **III. Conclusion**

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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